

**EXHIBIT A**  
**CLAIMS WHEN FILED (09/700,967; 4100.001400)**  
**AND SUBJECT TO RESTRICTION REQUIREMENT**

1. A purified protamine that is bioactive, that has a low molecular weight and that has reduced immunoresponsiveness or toxicity compared to native protamine.
2. The protamine of claim 1, wherein said bioactive protamine is a salmine protamine.
3. The protamine of claim 1, wherein said bioactive protamine is a clupeine protamine.
4. (Amended) The protamine of claim 1, wherein said bioactive protamine has a molecular weight of between about 400 and about 2500 Daltons.
5. The protamine of claim 4, wherein said bioactive protamine has a molecular weight of between about 450 and about 1500 Daltons.
6. The protamine of claim 5, wherein said bioactive protamine has a molecular weight of between about 500 and about 1350 Daltons.
7. The protamine of claim 6, wherein said bioactive protamine has a molecular weight of between about 1100 and about 1300 Daltons.
8. The protamine of claim 7, wherein said bioactive protamine has a molecular weight of about 1200 Daltons.
14. (Amended) A composition comprising at least a first purified bioactive protamine in accordance with claim 1.
15. The composition of claim 14, wherein said composition comprises at least a first and at least a second purified bioactive protamine.
16. The composition of claim 15, wherein said composition comprises a plurality of purified bioactive protamines.

17. (Amended) The composition of claim 14, further comprising at least one additional biologically active agent.
18. (Amended) The composition of claim 17, further comprising at least one additional coagulant.
19. (Amended) The composition of claim 17, further comprising at least a first therapeutic protein or polypeptide.
20. The composition of claim 19, further comprising insulin.
21. The composition of claim 20, further comprising recombinant insulin.
22. (Amended) The composition of claim 20, further comprising human insulin.
23. (Amended) The composition of claim 14, wherein said composition is a pharmaceutical composition.
24. (Amended) The composition of claim 23, wherein said pharmaceutical composition is formulated for injection.
35. (Amended) A method of preparing at least a first bioactive protamine, that has a low molecular weight and that has reduced immunoresponsiveness or toxicity compared to native protamine, comprising contacting a native protamine composition with at least a first proteolytic composition comprising an amount of at least a first proteolytic enzyme effective to produce said at least a first bioactive protamine.
36. The method of claim 35, wherein said at least a first proteolytic composition comprises at least a first thermolysin enzyme.
37. (Amended) The method of claim 35, wherein said at least a first proteolytic composition comprises at least a first ficin enzyme.
38. (Amended) The method of claim 35, wherein said at least a first proteolytic composition comprises at least a first collagenase enzyme.

39. (Amended) The method of claim 35, wherein said at least a first proteolytic composition comprises at least a first kallikrein enzyme.

40. (Amended) The method of claim 35, wherein said at least a first proteolytic composition comprises at least a first proline-specific endopeptidase enzyme.

41. (Amended) The method of claim 35, wherein said at least a first proteolytic composition comprises at least a first and at least a second proteolytic enzyme.

42. (Amended) The method of claim 35, wherein said at least a first proteolytic enzyme is removed after said at least a first bioactive protamine is produced.

43. (Amended) The method of claim 35, wherein at least a first and a second bioactive protamine is produced.

44. (Amended) The method of claim 35, wherein a plurality of bioactive protamines are produced.

45. (Amended) The method of claim 35, wherein the at least a first bioactive protamine produced has a molecular weight of between about 450 Daltons and about 1350 Daltons.

46. (Amended) The method of claim 35, further comprising formulating the at least a first bioactive protamine produced in a pharmaceutically acceptable composition.

48. A method of selecting an improved low molecular weight protamine species or fraction, comprising selecting from a plurality of low molecular weight protamine species or fractions a low molecular weight protamine species or fraction that substantially retains the bioactivity of native protamine and that has substantially reduced immunoresponsiveness or toxicity compared to native protamine.

49. The method of claim 48, wherein said plurality of low molecular weight protamine species or fractions are prepared by contacting a native protamine composition with at least a first proteolytic enzyme.

50. (Amended) The method of claim 48, further comprising formulating the improved low molecular weight protamine species or fraction selected in a pharmaceutically acceptable composition.

52. (Amended) A kit comprising at least a first container that comprises at least a first purified bioactive protamine in accordance with claim 1.

53. (Amended) The kit of claim 52, further comprising at least one additional anticoagulant.

54. The kit of claim 53, wherein said at least one anticoagulant is heparin or low molecular weight heparin.

55. (Amended) A method of inactivating heparin or low molecular weight heparin, comprising contacting heparin or low molecular weight heparin with a biologically effective amount of at least a first purified bioactive protamine in accordance with claim 1.

56. The method of claim 55, wherein said heparin or low molecular weight heparin is located within a mammal and said composition is administered to said mammal.

57. (Amended) A method of ameliorating an effect of heparin or low molecular weight heparin in a mammal, comprising administering to said mammal a therapeutically effective amount of at least a first pharmaceutical composition comprising at least a first purified bioactive protamine in accordance with claim 1.

58. (Amended) A method for treating or preventing undue or excessive bleeding in a mammal, comprising administering to a mammal having or at risk for developing excessive bleeding a therapeutically effective amount of at least a first pharmaceutical composition comprising at least a first purified bioactive protamine in accordance with claim 1.

59. (Amended) The method of claim 58, wherein said mammal exhibits excessive bleeding associated with systemic heparinization.

60. (Amended) The method of claim 58, wherein said mammal exhibits excessive bleeding associated with extracorporeal blood circulation.

61. (Amended) The method of claim 58, wherein said mammal exhibits excessive bleeding associated with a disease or disorder.

62. (Amended) The method of claim 58, wherein said mammal exhibits excessive bleeding associated with a trauma or surgery.

63. (Amended) The method of claim 58, wherein at least a second coagulant is further administered to said mammal.

64. (Amended) A method of prolonging the bioavailability of insulin upon administration to a mammal, comprising co-administering insulin to a mammal in combination with an effective amount of a protamine composition that comprises at least a first purified bioactive protamine in accordance with claim 1.

65. (Amended) A method for treating or preventing diabetes in a mammal, comprising administering insulin to a mammal having or at risk for developing diabetes in combination with a therapeutically effective amount of a protamine composition that comprises at least a first purified bioactive protamine in accordance with claim 1.

66. (Amended) The method of claim 64, wherein said insulin and said protamine composition are administered to said mammal in a single pharmaceutical composition.

67. (Amended) The method of claim 64, wherein said insulin and said protamine composition are administered to said mammal in distinct pharmaceutical compositions.

68. (Amended) The method of claim 56, wherein said mammal is a human subject.